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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,746	12/26/2001	Ronald W. Pero	63596-A CCD	1899

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Mintz,Levin,Cohn,Ferris,Glovsky&Popeo PC
One Financial Center
Boston, MA 02111

EXAMINER
GUZO, DAVID

ART UNIT	PAPER NUMBER
1636	4

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/034,746	Applicant(s) PERO ET AL.	
	Examiner David Guzo	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/26/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Detailed Action

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants claim a method for treating immunosuppression in a warm-blooded animal comprising administering combretastatin A4, prodrugs thereof and mixtures thereof effective to induce immune responsiveness without causing vascular destruction. Applicants also claim a method of treating a warm-blooded animal bearing a tumor comprising administering immunotherapy (or immuno-gene therapy) to inhibit or kill tumor cells while administering combretastatin A4, prodrugs or mixtures thereof in an amount effective to enhance immune responsiveness.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These

factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following: 1) Unpredictability of the art. It is noted that combretastatin was originally identified in the prior art as a potential anti-tumor agent (when used at high dosages) because of its antivascular activity against tumor vasculature. Applicants' invention however involves use of combretastatin (optionally in combination with immunotherapy) at low dosages below those which result in vasculature destruction in the tumor. Applicants indicate that low dosages of combretastatin (in combination with immunotherapy) act to enhance the host immune response against the tumor and can result in an effective host immune response against the tumor. The art with regard to the traditional (antivascular) use of combretastatin for treatment of cancer is unpredictable. Indeed, Tozer et al. (Cited by applicants, Cancer Research, 1999, Vol. 59, pp. 1626-1634) notes that prior to combretastatin being used effectively, "...further information is required regarding its mechanism of action and vascular effects under *in vivo* conditions." (Tozer et al., p. 1626, right column, last paragraph). With regard to the ability of low dosages of combretastatin to affect host immunosuppression in a manner sufficient to result in a therapeutically effective outcome in treating naturally occurring cancers, it is noted that this has not been demonstrated. Applicants have presented some *in vitro* data and data involving tumor cells injected into experimental rats; however, it is unclear if the enhancement of the immune response would be sufficient to result in a therapeutically effective result in humans or animals suffering from naturally occurring cancers. Applicants have presented no art recognized correlation between the results obtained

using the *in vitro* or animal models and the results which the skilled artisan would reasonable expect to see in humans or other warm blooded animals suffering from naturally occurring tumors. Indeed, with regard to use of murine models to identify human drugs, Gura (Science, 1997, Vol. 278, pp. 1041-1042) notes that results obtained in cell and animal models are often not predictive at all with regard to the effectiveness of the drug in humans.

With regard to the use of immunotherapy in concert with administration of combretastatin, it is noted that "Cancer immunotherapy is yet to be realized as a therapeutic approach in the oncologist's armamentarium." (Gomez-Navarro et al., European Journal of Cancer, 1999, Vol. 35, No. 6, pp. 867-885, p. 879, bottom right column). Given that the prior art indicates that neither combretastatin nor immunotherapy has yet been shown to be effective in vivo for treating cancer, it must be considered that use of a combination of the two unsuccessful treatments to treat cancers would be unpredictable at best.

2) State of the art. The state of the art with regard to use of combretastatin and/or immunotherapy for successful treatment of cancer is poorly developed with no unambiguous demonstrated successes at the time of applicants' invention.

3) Number of working examples. Applicants present no working examples of the claimed invention. Applicants do provide some *in vitro* data and some *in vivo* data involving experimental rat systems; however, applicants provide no correlation between said results and the results which the skilled artisan would expect to see in humans or in animals suffering from naturally occurring cancers.

4) Amount of guidance presented by applicants. Applicants provide some in vitro and rat in vivo data but do not provide evidence that the results would translate to therapeutically relevant results in humans or animals suffering from naturally occurring cancers. Also, applicants do not provide a disclosed or art recognized correlation or nexus between the results obtained in the in vitro or rat in vivo systems and results which the skilled artisan would reasonably expect to obtain in humans or warm blooded animals.

5) Scope of the invention. The scope of the invention is broad, with the claims reading on treating immunosuppression in any warm-blooded animal or treating any warm-blooded animal suffering from any tumor.

6) Nature of the invention. The invention involves one of the most complex areas of biology/medicine; the treatment of cancers using novel anticancer compounds or immuno-gene therapy.

7) Level of skill in the art. The level of skill in the art is high; however, given the unpredictability of the art, the poorly developed state of the art, the lack of guidance provided by applicants and the prior art and the broad scope of the claimed subject matter, it must be considered that the skilled artisan would have needed to have conducted trial and error experimentation in order to try to reduce the instant invention to practice.

Given the above factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that the

skilled artisan would have had to have conducted undue and excessive experimentation in order to reduce the claimed invention to practice.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4 and 14 (and dependent claims) are vague in that applicants recite a "composition" which can be combretastatin A4. It is unclear how a single compound can be a composition since a composition is made up of two or more components.

The term "substantial" in claims 9 and 14 is a relative term which renders the claim indefinite. The term "substantial" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear how the skilled artisan would distinguish between a dosage of combretastatin which would result in a "substantial" destruction of tumor vasculature vs. a dosage which would result in a non-substantial destruction of tumor vasculature. For example, would a 30% destruction of tumor vasculature be "substantial" or would "substantial" mean greater than 50% destruction of the tumor vasculature, etc.?

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Faxes may be sent directly to the examiner at (703) 746-5061.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David Guzo
May 2, 2003